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09/688,566	10/16/2000	Dasa Lipovsek	50036/021004	1736

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CLARK & ELBING LLP  
101 FEDERAL STREET  
BOSTON, MA 02110

EXAMINER
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AUDET, MAURY A

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Appli ation No.

09/688,566

Applicant(s)

LIPOVSEK ET AL.

Examiner

Maury Audet

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-- The MAILING DATE of this communication app ars on the cover she t with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 12 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-43 is/are pending in the application.
- 4a) Of the above claim(s) 26-31 and 33-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-26 and 32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,5,7,9.
- 4) ☒ Interview Summary (PTO-413) Paper No(s). 19.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: IDS Paper No. 14.

## DETAILED ACTION

### Election/Restriction

Applicant's election without traverse of claims 1-25, and 32 and fibronectin as the non-antibody protein species in claim 32 is acknowledged.

### Rejections

#### 35 U.S.C. § 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25<sup>32</sup> are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

*Vas-Cath Inc. V. Mahurka*, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117).

The claimed invention, and claims 1-24, is primarily drawn to “a non-antibody protein comprising a domain having an immunoglobulin-like fold, said non-antibody protein deriving from a reference protein (elected species fibronectin (claim 32)) having a mutated amino sequence wherein said non-antibody protein binds with a  $K_d$  at least as tight as  $1\ \mu\text{M}$  to a compound that is not bound as tightly by said reference protein” (claims 1-22), wherein the derivative protein is immobilized to a solid support (claims 23-25).

The specification describes 103 peptide sequences (SEQ ID NOS: 38-140), derived from fibronectin III (FN3) (tenth domain) (page 12; see also page 36, describing “10Fn3-based master library”). Specification pages 35 (last ¶), 54 (2<sup>nd</sup> ¶), and 56 (2<sup>nd</sup> ¶), for example, describe that TNF- $\alpha$  performed binding of RNA-protein fusion from the master library (see also page 53 “Fn-binders specific for the protein, TNF- $\alpha$ ”). Additionally, beyond the reference protein, no other binding “compound” was found to be described in the specification other than TNF- $\alpha$ . Certain examples of specific sequences binding to the TNF- $\alpha$  are described in the specification, and indication that some of the 169 total peptide sequences do not or do not bind at the level desired by the invention are also described. [It is unclear whether all of the 103 sequences (SEQ ID NOS: 138-140) are capable of binding to TNF- $\alpha$  at the levels desired/claimed, because the specific binding levels themselves are unclear, as discussed below.]

However, nowhere was it found in the specification that any of the potential 42 reference proteins listed in claim 32, other than fibronectin, as capable of yielding the derived non-antibody protein of the invention, were actually mutated and tested for greater capacity to bind a compound and ultimate formulation as one of the listed 106

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SEQ ID NOS: 38-140 (specification page 12). Applicant must point out where in the specification it can be found that Applicant mutated an amino acid sequence of a reference protein, other than fibronectin, to yield a derived non-antibody protein capable of binding a compound as claimed.

One of skill in the art would not recognize from the disclosure that Applicant was in possession of any non-antibody protein derived from any reference protein, or even any of the 42 reference proteins of claim 32, other than fibronectin; having any mutated amino acid sequence capable of binding a compound with greater strength than the reference protein as claimed, other than the specific derived proteins described in the specification as capable of binding with a distinct tightness (yet unclear as discussed below). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116). Namely, only a few specific non-antibody proteins derived from a fibronectin reference protein have been described as being as meeting at least some of the claim limitations.

Thus, neither the claims nor the specification describes the non-antibody proteins of the invention. Since it is unknown what non-antibody proteins, or even which specific non-antibody proteins and/or sequences described in the specification, specifically meet the claimed limitations, it cannot be ascertained whether Applicant had the claimed non-antibody proteins (claim 1). One of skill in the art would not recognize from the disclosure that Applicant was in possession of any "non-antibody protein" mutated from any reference protein, and capable of binding a compound tighter than the latter.

**35 U.S.C. § 112, 2nd**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-~~7~~<sup>432</sup> are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, it is unclear what specific protein(s) is contemplated as “a non-antibody protein”? The specification very broadly defines “non-antibody protein” on page 12 and describes 106 sequences (SEQ ID NOS: 38-140), derived from fibronectin III (FN3) (see also specification page 36, describing “10Fn3-based master library”; see also originally filed claims 41 and 43, and Fig. 25, drawn to a mutated loop structure on Fn3 (SEQ ID NOS: 38-140)). However, none of the 106 sequences, some or all tested for binding capacity versus the Fn3 reference protein, have been distinctly claimed in the elected claims. Therefore it is unclear what Applicant is referring to simply by claiming a “non-antibody protein”, which necessarily reads on any protein other than an antibody?

In claim 1, it is unclear what specific protein(s) is contemplated as “a reference protein”. The specification describes 106 sequences (SEQ ID NOS: 38-140), derived from fibronectin III (FN3). However, “fibronectin” or “FN3”, or a similar characterization has not been distinctly claimed. Therefore, it is unclear what “a reference protein” refers to, since any protein, even an antibody, could constitute a reference protein.

In claim 1, it is unclear what is contemplated by “a mutated amino acid sequence”? The specification describes 106 sequences (SEQ ID NOS: 38-140), derived from fibronectin III (FN3). A cursory examination of the sequences was performed using a computer readable format “multiple alignment” test to determine if a distinguishable

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core sequence was largely present in the 106 peptide sequences. This was not found, hence a painstaking sequence by sequence and residue by residue analysis between the derived peptide sequence residues and the mutated fibronectin reference protein residues would have to be performed to determine what “a mutated amino acid sequence” constitutes within the metes and bounds of the claim language. In addition to not distinctly claiming what “a non-antibody protein” and what “a reference protein” constitute within the invention; it is unclear where or with what amino acids, an unnamed “reference protein” domain of sequence has been mutated.

In claim 1, it is unclear what is contemplated by “a compound”? The specification describes 106 sequences (SEQ ID NOS: 38-140), derived from fibronectin III (FN3). Specification pages 35 (last ¶), 54 (2<sup>nd</sup> ¶), and 56 (2<sup>nd</sup> ¶), for example, describe that TNF- $\alpha$  performed binding of RNA-protein fusion from the master library (see also specification page 53 “Fn-binders specific for the protein, TNF- $\alpha$ ”). No other binding “compound” was found to be described in the specification. However, since neither the “reference protein” or “non-antibody protein” have been distinctly claimed, it is not only unclear as claimed what the invention’s “proteins” are, but also unclear what “compound” can be bound to both the “reference [and] non-antibody proteins”? Furthermore, since the “reference protein” has been mutated, it is unclear whether the same “compounds”, additional “compounds”, less “compounds”, or entirely different “compounds, could then bind to the “proteins” as contemplated by the invention? Not only must the “proteins” be distinctly claimed, so to must the “compounds” capable of binding to the “proteins”.

In claims 1-8, it is unclear what "Kd" level of tightness the "proteins" are capable of binding to the "compound". The language of claim 1 is drafted in singular form; namely "[a] non-antibody protein", "an immunoglobulin-like fold", "a reference protein", "a mutated amino acid sequence", "said non-antibody protein", "a compound", "said reference protein". Additionally claim 1 recites that the singular "non-antibody protein" with a single "mutated amino acid sequence" is capable of binding "at least as tight as 1  $\mu$ M to a compound". Claims 2-8 then list in the alternative, all the different levels of binding this one "mutated amino acid sequence" is capable of binding to an undefined "compound". Based on both claim 1 and claims 2-8, it is unclear how a single "mutated amino acid sequence" is capable of binding to a single unnamed "compound", with so many different levels of tightness, when only one amino acid sequence has been mutated? Specification page 6 describes that "[a]gain, these proteins are characterized by their ability to bind to compounds that are not bound or are not bound as tightly by the corresponding naturally-occurring fibronectin domain"; however, this *sheds no light on what distinct non-antibody protein(s), of the claimed invention, bind in such a way.* Applicant is asked to specifically point out in the specification, which distinct non-antibody protein(s) and their sequence(s) binds to TNF- $\alpha$ , to yield the binding level limitations of claims 1-8.

In claims 9-11, it is unclear how many non-antibody protein loops are needed to contribute to binding, to confer the desired tightness (which as noted above is unclear), between a "non-antibody [derivative] protein" and a "compound". The claims indicate that the derivative protein contains one, two, or three loops and that at least one, or at least two, or three of the loops contribute to binding. It was not found in the specification



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whether one, two, or three loops are needed to bind a "compound", in order to confer the desired level of tightness? Therefore, it is unclear how many loops actually have to be mutated in order to confer the levels of tightness (depending on how this is defined), to carry out the invention? Applicant is asked to specifically point out in the specification where the above has been described.

Regarding the above rejections, it is strongly suggested that Applicant amend the claims to distinctly claim the distinct non-antibody protein (i.e. Fn3 with tenth domain mutated to distinct SEQ ID NOS:); the distinct reference protein (Fn3) the former is derived from; the distinct mutated amino acid sequence(s) of the distinct loops mutated; the distinct amount of loops (one, two, or three) to allow the desired Kd binding; the distinct desired level of tightness; and the distinct compound to which the "proteins" [derived and reference] binds.

Additionally, it is asked that Applicant specifically point out which "non-antibody proteins" derived from a mutated "reference protein" were tested and found to bind as claimed (i.e. by page and where applicable, and SEQ ID NOS:).

### 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the

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international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-8, 12-19, 21-25, and 32 are rejected under § 102 (b), as anticipated by Koide et al. ("Koide et al. #1"; FASEB Journal; Abstract, July 31, 1997).

Koide et al. #1 teach a non-antibody protein (monobody) having an immunoglobulin-like fold, said non-antibody protein deriving from a reference protein (Fn3, lacking disulfide bonds) by having a mutated amino acid sequence (randomized); wherein said non-antibody protein binds with a Kd at least as tight as 1  $\mu$ M ("significant affinities"); wherein said reference protein is a naturally-occurring mammalian protein (Fn3); wherein said derivatized protein is immobilized to a solid support (intrinsic since panning techniques used to bind protein to target molecule/antigen [i.e. compound] immobilized to some solid support known in the art) (abstract).

For Koide et al., #1, it is intrinsic, or through routine protein purification by one of skill in the art, that the mutated Fn3 of Koide et al. #1 would achieve the loop binding of Applicants claims 9-11; a disulfide bond in the derivative protein for stability as a result of the selected amino acid substitutions (Applicant's claim 13); the immunoglobulin-like fold mass between 7.5-10 kD of Applicant's claim 14-16; the dimer of Applicant's claim 18 (through monomer binding); and the immunoglobulin-like fold consisting of 50-150 amino acids of Applicant's claims 21-22; since Koide et al. #1 use the same reference protein, Fn3, for mutation to a derived non-antibody protein.

Claims 1-8, 13-17, and 21-25 are rejected under § 102 (b), as anticipated by McConnell et al. (J. Mol. Biol., 1995).

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McConnell et al. teach a non-antibody protein having an immunoglobulin-like fold (“strands . . . overall structure is similar to an immunoglobulin fold”; page 463, column 2, lines 3-5), said non-antibody protein deriving from a reference protein (Tendamistat, *Streptomyces tendae*); by having a mutated amino acid sequence (randomizing residues; page 463, column 2); wherein said non-antibody protein binds with a  $K_d$  at least as tight as 1  $\mu\text{M}$  (nM and pM affinities; see page 466, column 2, 2<sup>nd</sup> ¶, last 2 lines; and Table 2); wherein the derivative protein has at least one disulfide bond (Tendamistat has two; page 463, column 2); wherein the domain having the immunoglobulin-like fold consists of approximately 5-150 amino acids (74 amino acid; abstract); wherein said derivatized protein is immobilized to a solid support (intrinsic as part of affinity binding tests to target molecule [i.e. “compound”], Table 2). [For McConnell et al., it is intrinsic, or through routine protein purification by one of skill in the art, that the derived protein form the dimer of Applicant’s claim 18 (through monomer binding)].

Claims 1-8, 12; 14-18, and 21-25 are rejected under § 102 (b), as anticipated by Nord et al. (Nature Biotechnology, August 1997).

Nord et al. teach a non-antibody protein having an immunoglobulin-like fold (individually folded; binds to immunoglobulins), said non-antibody protein deriving from a reference protein (staphylococcal protein A (SPA); by having a mutated amino acid sequence (multiple random amino acid substitutions) (page 772, 3<sup>rd</sup> ¶); wherein said non-antibody protein binds with a  $K_d$  at least as tight as 1  $\mu\text{M}$  (“found to be in the  $\mu\text{M}$  range”; page 774, 1<sup>st</sup> ¶, last s.); wherein the reference protein lacks disulfide bonds (not found in

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reference description and absent evidence to the contrary); wherein the domain having the immunoglobulin-like fold consists of approximately 5-150 amino acids (“approximately 58 amino acids”; page 772, 3<sup>rd</sup> ¶); wherein said derivatized protein is immobilized to a solid support (sensor used to bind protein to target molecule/antigen [i.e. compound]) (page 774, 1<sup>st</sup> ¶, lines 3-4). [For Nord et al., it is intrinsic, or through routine protein purification by one of skill in the art, that the derived protein form the dimer of Applicant’s claim 18 (through monomer binding)].

Claims 1-25, and 32 are rejected under § 102 (e), as anticipated by Koide et al. (“Koide et al. #2”; US 6462182).

Koide et al. #2 teach a non-antibody protein (monobody) having an immunoglobulin-like fold, said non-antibody protein deriving from a reference protein (Fn3, lacking disulfide bonds) by having a mutated amino acid sequence ; wherein said non-antibody protein binds with a Kd at least as tight as 1  $\mu$ M (column 5, lines 39-40; Koide et al. teach Applicant’s claims 1-8 from the opposite direction: as the dissociation constant [Kd] of non-antibody protein:compound is 10<sup>(-6)</sup> moles/liter; see page 37, lines 26-29, “binding affinities of monobodies on phage surfaces” to a target molecule/antigen [i.e. compound] using known techniques); wherein the derivative protein contains at least one mutated loop (column 4, lines 29-32); wherein said reference protein is a naturally-occurring mammalian protein (human Fn3; column 11, line 18); and wherein said domain having an immunoglobulin-like fold is mutated and comprises up to 34% mutated amino acids as compared to the immunoglobulin-like fold of said reference protein (at least 50% homology; column 4, line 33-34); and wherein said derivatized protein is immobilized to

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a solid support (column 26, lines 43-62, upon binding to a target molecule/antigen [i.e. compound] immobilized to a microtiter dish [which Applicant teach on specification page 15 is equivalent to solid supports such as a bead or microchip]).

For Koide et al., #2, it is intrinsic, or through routine protein purification by one of skill in the art, that the mutated Fn3 of Koide et al. #2 would achieve the loop binding of Applicants claims 9-11; a disulfide bond in the derivative protein for stability as a result of the selected amino acid substitutions (see, for example, Koide et al. #2's Fn3 mutation SEQ ID NOS: 49, 51, 55, 57 and 67, with CYS substitutions (containing sulfur functional group), allowing for intra-loop disulfide bonding or inter-loop disulfide bonding where one, two, or three loops contained, for example, any of the noted SEQ ID NOS.; like the intra- and inter-chain disulfide bonding by CYS in the insulin molecule). (Applicant's claim 13); the immunoglobulin-like fold mass between 7.5-10 kD of Applicant's claim 14-16; the dimer of Applicant's claim 18 (through monomer binding); and the immunoglobulin-like fold consisting of 50-150 amino acids of Applicant's claims 21-22; since Koide et al. #2 use the same reference protein, Fn3, for mutation to a derived non-antibody protein.

Claim 1-25, and 32 are rejected under 35 U.S.C. 102(f) because the applicant did not [clearly] invent the claimed subject matter, in view of WO 00/34784.

WO 00/34784, like the present invention, claims priority to US 60/111,737 (10.12.98), is licensed to Phylos, Inc., and is drawn to protein scaffolds for antibody mimics and other binding proteins, namely using the Fn3 domain as the reference protein for mutation of at least one randomized loop. However, WO 00/34784 lists only a single

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inventor (Lipovsek); whereas, the present application includes three inventors (Lipovsek, Wagner, and Kuimelis). Since the applications are claiming the same subject matter, stemming from the same provisional application, it is unclear who constitutes the inventive entity of the present application.

### 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide et al. ("Koide et al. #1"; FASEB Journal, Abstract, July 31, 1997) in view of Koide et al. ("Koide et al. #2" US 6462182).

The teachings of Koide et al. #1 and #2 are discussed above.

Koide et al. #1 do not specifically teach a derivative protein with one, two, or three mutated loops [Applicant's claims 9-11]; or a domain having an immunoglobulin-like fold that is mutated and comprises up to 34% mutated amino acids as compared to the immunoglobulin-like fold of said reference protein. [Applicant's claim 20]

Koide et al. #2 teach a derivative protein that contains at least one mutated loop (column 4, lines 29-32); and a domain having an immunoglobulin-like fold is mutated and comprises up to 34% mutated amino acids as compared to the immunoglobulin-like fold of said reference protein (at least 50% homology; column 4, line 33-34).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to mutate the reference protein of Koide et al. #1 as Koide et al. #2, because Koide et al. #1 and #2 are teaching the mutation of the same reference protein for the benefit of compound binding, as an alternative to the use of immunoglobulins.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-25, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide et al. ("Koide et al. #1"; FASEB Journal, Abstract, July 31, 1997) and Koide et al. ("Koide et al. #2" US 6462182) in view of McConnell et al. (J. Mol. Biol., 1995).

Koide et al. #2 teach for example, Fn3 mutation SEQ ID NOS: 49, 51, 55, 57 and 67, with CYS substitutions (containing sulfur functional group), allowing for intra-loop disulfide bonding or inter-loop disulfide bonding where one, two, or three loops contained, for example, any of the noted SEQ ID NOS:) (like the intra- and inter-chain disulfide bonding by CYS in the insulin molecule). However, Koide et al. #1 or Koide et al. #2 do not specifically teach a derivative protein with disulfide bonds (i.e. from a mutated Fn3 reference protein that lacks disulfide bonds). [Applicant's claim 13].

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McConnell et al. teach that the beta-sheets of Tendamistat, a protein scaffold, contain two disulfide bonds, accounting for the overall stability of the protein [immunoglobulins contain a single disulfide bond] (page 463, column 2, lines 5-7).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to purify the protein of Koide et al. #1 and #2 with amino acid substitutions (i.e. using CYS SEQ ID NOS: as noted above in Koide et al. #2, and standard biochemical purification techniques during compound mutation/synthesis) to allow for formation of disulfide bonds within the derived protein, because McConnell et al. teach that Tendamistat, a protein scaffold, attains considerable stability of the overall scaffold, a desired quality of protein scaffolds, with the disulfide bond(s).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maury Audet whose telephone number is 703-305-5039. The examiner can normally be reached from 7:00 AM – 5:30 PM, off Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at 703-306-3220. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-1234 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

MA

May 29, 2003

MICHAEL MELLER  
PRIMARY EXAMINER

